REMARKS

Claims 40, 42, 43, 103, and 111-151 are pending in the above-identified application. All claims stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by prior art references and/or 35 U.S.C. § 103(a) as allegedly obvious over prior art references.

With this Reply, Claims 40, 42, 43, 103, and 111-151 have been amended to correct minor typographical errors and inconsistent formatting. Additionally, Claim 42 has been amended to specify that the supplemental material imparts a characteristic selected from the group consisting of strength, resorption time, adherence, frictional characteristics, release kinetics, consistency, formability, tensile strength, hardness, fracture toughness, elasticity, and imaging capability to the composite. Support for this amendment is found in the specification at, for example, page 36, line 31 – page 45, line 6. None of these amendments introduces new matter. Favorable reconsideration and allowance of the pending claims in view of the remarks provided below are respectfully requested.

I. Rejections Under 35 U.S.C. §102(e) Over Constantz (U.S. Patent No. 5,962,028)

Claims 40, 42, 43, 103, 111-118, 120, 121, 127-131, 133-135, and 138-146 have been rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 5,962,028 to Constantz (hereinafter "Constantz"). The rejected claims may be classified in two general groups: (1) those directed to compressed powder objects that comprise powders of a calcium phosphate and a promoter and form poorly crystalline apatitic (PCA) calcium phosphate, methods for preparing such objects, and methods for treating a bone defect using such objects (Claims 40, 43, 103, 111-118, 120-121, 127-131, and 133-135) and (2) composite materials that include a poorly crystalline apatitic (PCA) calcium phosphate and methods of making molded

PCA calcium phosphate compositions (Claims 42 and 138-146). Applicants will first discuss the teachings of Constantz and then address its applicability to each of these claim groups separately.

Constantz teaches carbonated hydroxyapatite compositions (col. 4, lines 40-42). The carbonated hydroxyapatite compositions are formed by combining a phosphoric acid source, an alkali earth metal source (*e.g.,* calcium source), calcium carbonate, and a physiologically acceptable lubricant (col. 5, lines 7-13). The dry ingredients (*i.e.,* the phosphoric acid source, alkali earth metal source, and calcium carbonate) are mixed using mills or rollers "until a uniform dispersal of ingredients is obtained" (col. 5, line 66 – col. 6, line 7). The lubricant is then added to the mixed dry ingredients in an amount to form a flowable "paste" or moldable "clay-like putty" (col. 6, lines 10-36). The paste or putty hardens, and "during hardening, crystal growth occurs" (col. 6, lines 37-40). The hardened product is carbonated hydroxyapatite. Shaping of the composition may occur prior to, during, or after hardening of the paste or putty (col. 7, 60-62).

The Examiner suggests that Constantz anticipates the first group of claims identified above, which is directed to compressed powder objects and methods of their manufacture and use. Specifically, the Examiner interprets Constantz as suggesting that "[c]ompressed materials with high compressive strength can be formed by mixing dry ingredients (col. 6, top) and pressing (rolling), then hydrating (col. 6, paragraph 2)" (Office Action, page 2). Applicants respectfully disagree.

A claim is anticipated only when a prior art reference teaches each and every element of the claim. *See* MPEP § 2131. As used in the instant application and understood by those skilled in the art, "compressed" powder objects result from pressing or squeezing powders together by applying pressure. *See, e.g.,* RANDOM HOUSE WEBSTER'S COLLEGIATE DICTIONARY 279 (1992)

("**compressed** – *adj.* 1. pressed into less space; condensed...2. pressed together...3. flattened or as if by pressure..."); MCGRAW HILL DICTIONARY OF SCIENTIFIC AND TECHNICAL TERMS 427 (5th ed. 1994) ("**compression** – ... [MECH] Reduction in the volume of a substance due to pressure"). The claimed compressed powder objects are formed by subjecting powders of calcium phosphate and a promoter to pressure (Claims 40, 43, & 103; page 61, lines 26-27). Such pressure may be applied by, for example, a hand-held press or a hydraulic press (page 61, lines 19-27; page 88, line 20 – page 89, line 29). In contrast, the dry ingredients of Constantz's compositions are dispersed. Constantz itself unambiguously states that:

> Any or all of the dry ingredients may be added prior to the initiation of mixing or prior to the completion of mechanical mixing. Methods of mixing can include ball milling, Brabender mixing, rolling between one or more rollers and a flexible container, or the like. Preferably, mixing will be thorough and will occur for a relatively short time or until a uniform dispersal of ingredients it obtained.

(col. 5, line 66 – col. 6, line 9) (emphasis added). Thus, as indicated by this passage, Constantz utilizes rolling and milling to intermix and disperse the dry ingredients rather than press them together. The techniques referred to in this passage are conventional techniques for making free-flowing powders, not compressed powders. Accordingly, Constantz does not teach the claimed compressed powder objects, and Applicants, therefore, respectfully request that the novelty rejection of Claims 40, 43, 103, 111-118, 120-121, 127-131, and 133-135 be withdrawn.

The Examiner also suggests that Constantz anticipates the second group of claims identified above, which is directed to composites containing poorly crystalline apatitic calcium phosphate and methods of making molded poorly crystalline apatitic calcium phosphate compositions. Specifically, the Examiner states that "[a]patite with carbonate (col. 2, lines 35-54) provides for a bone substitute, a poorly crystalline apatite Ca/P (col. 4, last paragraph)" (Office Action, page 2). However, Constantz nowhere teaches a poorly crystalline apatitic

calcium phosphate. In fact, Constantz expressly acknowledges that his composition is a crystalline apatite:

> Compositions are provided that are comprised of substantially pure (greater than 80% by weight) dahllite-like compositions referred to as carbonated hydroxyapatite... The dahllite or francolite-like products can be readily formed by combining the wet and dry reactants to provide a substantially uniform mixture, shaping the mixture as appropriate, and allowing the mixture to harden. During hardening, the mixture crystallizes into a solid and essentially monolithic apatitic structure.

(col. 4, lines 40-52) (emphasis added).

Furthermore, as amended, independent Claim 42 recites that the poorly crystalline apatitic calcium phosphate includes a supplementary material that imparts a "characteristic selected from the group consisting of strength, resorption time, adherence, frictional characteristics, release kinetics, tensile strength, hardness, fracture toughness, elasticity, and imaging capability." Constantz lacks any teaching that supplemental materials capable of altering these mechanical properties may be added to his carbonated hydroxyapatite compositions. Instead, Constantz suggests only the addition of fluoride or pharmacologically active agents to the carbonated hydroxyapatite (col. 6, line 62 – col. 7, line 8; col. 8, lines 24-26). Thus, amended Claim 42 is further distinguishable over Constantz.

Given that Constantz fails to disclose either a poorly crystalline apatitic calcium phosphate or the addition of supplemental materials to alter mechanical properties of a composite, Applicants submit that the novelty rejection of Claims 42 and 138-146 cannot be sustained.[1]

[1] Applicants further note that the Examiner mistakenly characterizes demineralized bone and collagen as the same material at page 3 and page 4 in the present Office Action. Demineralized bone and collagen are, in fact, distinct substances with different compositions and functions. *See, e.g.,* Mizuno, S. *et al.* (1992) "A Collagen/DBP Sponge System Designed for *In Vitro* Analysis of Chondroinduction." *Mat. Res. Soc. Symp. Proc.* 252:133-140; Mizuno, S. *et al.* (1996) "Three-Dimensional Composite of Demineralized Bone Powder and Collagen for *In Vitro* Analysis of Chondroinduction of Human Dermal Fibroblasts." *Biomaterials* 17:1819-1825, both of which are submitted herewith.

II. Rejections Under 35 U.S.C. §103(a) Over Constantz (U.S. Patent No. 5,962,028)

Claims 40, 42, 43, 103, 111-118, 120-123, 125, 127-131, 133-147, and 149-151 have been rejected under 35 U.S.C. §103(a) as allegedly obvious over Constantz. The teachings of Constantz are discussed above.

As an alternative to the novelty rejection, the Examiner suggests that both the first and second groups of claims are obvious in view of Constantz. The Examiner makes the following references to the claimed compressed powder objects and poorly crystalline apatitic calcium phosphate:

> The density and compression [of the claimed compressed powder objects would be the same of those disclosed in Constantz] as the Constantz products are of the density and compression (col. 10) as would result from use of the equipment, presses, disclosed at col. 8, line 43.... Although no specific structural geometry is identified, the fact that dry ingredients are combined and mixed (col. 8, lines 3-21) speaks for at least a powder or shaped form, of Apatitic CaP; the instant claim 43 compositions. See also col. 9, line 5 – free flowing mixes.

(Office Action, pages 3-4). Applicants submit that the teachings of Constantz cited by the Examiner are insufficient to sustain the obviousness rejections.

To establish a case of *prima facie* obviousness, the cited references must teach or suggest every claim limitation, and the prior art must provide a motivation to combine the cited references as well as a reasonable expectation of success upon doing so (MPEP § 2142). With respect to the first group of claims, Constantz does not teach or suggest that the powder components of the compositions disclosed therein may be compressed. The passages cited by the Examiner as disclosing compression from the use of presses teach only milling of the powder components to intermix them:

> Mechanical mixing may be by any form that results in an intimate mixing of the reactants. A variety of equipment may be used for these purposes including ball mills, planetary mills, centrifugal mills, mechanofusion systems, air pulverizers, jet mills, vibratory mills, colloid mills, attrition mills, disc mills, and the like.

(col. 8, lines 38-43). There is no mention, in this passage or elsewhere in Constantz, of presses or other equipment capable of compressing powders. The mixing techniques identified by Constantz are conventional techniques for producing uniformly-dispersed, free-flowing powders, not compressed materials. The distinction between milling materials to form powders and compressing powders is nontrivial because of the resultant difference in the strength of the powder product; compressed powders are stronger than those that have merely been milled. Thus, although Constantz mixes dry ingredients to produce a free-flowing powder composition, there is no suggestion that the powder is compressed or otherwise shaped. In fact, Constantz teaches that only the hydrated paste may be shaped (col. 4, lines 47-54; col. 9, lines 58-64). Given, therefore, that Constantz fails to teach or suggest a limitation of independent Claims 40, 43, and 103, *i.e.*, a compressed powder object, Applicants request the withdrawal of the obviousness rejection of the first group of claims.

With respect to the second group of claims, the Examiner states merely that the combination and mixing of dry ingredients speaks for a shaped form of apatitic calcium phosphate (Office Action, page 4, as quoted above). As discussed *supra* at Section I, Applicants emphasize that the explicit language of Constantz teaches only a crystalline apatite. Constantz contains no teaching or suggestion of a poorly crystalline apatitic calcium phosphate, as recited in independent Claims 42 and 138. Moreover, Constantz nowhere teaches or suggests the addition of supplemental materials capable of imparting the selected characteristics specified in amended Claim 42. In view of the teachings of Constantz and the limited rationale provided by the Examiner at pages 3-4 of the present Office Action in support of this rejection, Applicants submit that the obviousness rejection of the second group of claims should also be withdrawn.

III. Rejections Under 35 U.S.C. §102(e) Over Brown *et al.* (U.S. Patent No. 6,201,039)

Claims 40, 42, 43, 103, 111-120, 126-134, 138-145, and 148 have been rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,201,039 to Brown *et al.* (hereinafter "Brown"). In a manner similar to that provided, *supra*, at Section I, the rejected claims may be classified in two general groups: (1) those directed to compressed powder objects that comprise powders of a calcium phosphate and a promoter and form poorly crystalline apatitic (PCA) calcium phosphate, methods for preparing such objects, and methods for treating a bone defect using such objects (Claims 40, 43, 103, 111-120, and 126-134) and (2) composite materials that include a poorly crystalline apatitic (PCA) calcium phosphate and methods of making molded PCA calcium phosphate compositions (Claims 42, 138-145, and 148). For purposes of clarity, the teachings of Brown will be discussed and then applied to these two groups of rejected claims.

Brown teaches a method of producing polymineralic precursor particles that form hydroxyapatite in the absence of additional sources of calcium and phosphate (col. 5, lines 48-50). These precursor particles are formed by reacting at least one calcium source with at least one acid phosphate source in a nonaqueous liquid (col. 5, lines 52-59). A polymeric material capable of promoting mineralization of hydroxyapatite is added to either the nonaqueous liquid or to an aqueous phase combined with the precursor particles prior to their use *in vivo* (col. 12, lines 8-16).

The Examiner suggests that the teachings of Brown anticipate the first group of claims, which is directed to <u>compressed</u> powder objects and methods of their manufacture and use. Specifically, the Examiner states:

> CaP and the instant (claim 118) promoter, (although the word promoter is not used), Ca Carbonate, are mixed powder, resulting in a formed product – 2-5 micron powder (col. 13, lines 37-49)....Pellets are formed in Example 13. Addition of CaP to a promoter, a second calcium source, and pressing (claim 40)

> is seen as accomplished by the mixing; added water is not seen as required after formation of an object;...Further shaping, setting and formation into pellets or implantable forms of the shape of the bone to be repaired is shown by Brown – Examples 12, 13.

(Office Action, page 4). Applicants respectfully disagree.

As discussed previously in the context of Constantz, a compressed powder object is one in which the powder components have been pressed or squeezed together by the application of pressure. In contrast, during mixing, components need not be pressed together and, in fact, are frequently dispersed. This fundamental difference is evidenced by Brown's description of the preparation of the polymineralic precursor particles:

> In a typical run to prepare polymineralic particle precursors of hydroxyapatite which will be employed to form $Ca_9HPO_4(PO_4)_5OH$ in vivo, 127 g of $Ca(H_2PO_4)H_2O$ are reacted with 366 g of $Ca_4(PO_4)_2O$. The $Ca_4(PO_4)_2O$ is prepared by firing an intimate mixture of equimolar amounts of $CaCO_3$ and $CaHPO_4$ powder to 1400° C for 4 hours. After cooling the $Ca_4(PO_4)_2O$ is ground to an average particle size of 2-5 μm using standard powder preparation techniques. This material is then reacted with the acidic phosphate source $Ca(H_2PO_4)\cdot H_2O$, which is commercially available, by placing it and $Ca_4(PO_4)_2O$ in a 1-liter polyethylene bottle with approximately 400 ml of heptane.
>
> Approximately 250 g of zirconia or alumina, or 100 g polycarbonate pellets are added and the bottle is sealed. The presence of the pellets limits agglomeration. This bottle is then placed in any shaking or rolling device. In the reaction, all of the $Ca(H_2PO_4)\cdot H_2O$ and some of the $Ca_4(PO_4)_2O$ are consumed in the formation of the polymineralic precursor particles comprising $Ca_4(PO_4)_2O$ and $Ca_x(PO_4)_y$. These produced polymineralic particles can then react rapidly in the presence of water to form hydroxyapatite *in vivo*.

(col. 13, lines 38-55) (emphasis added). Thus, Brown's dry ingredients are ground to achieve small particle size and then shaken in a manner that specifically prevents agglomeration, or coming together, or the dry component particles. Applicants note that Brown's references to "pellets" in both Examples 12 and 13, as in the above-quoted passage, are directed to substances added to the powder mixture to prevent its agglomeration rather than the resultant form of the powders themselves. Consequently, Brown does not teach compressed powder objects and, in

fact, teaches away from pressing together or associating powders (as in, for example, compressed powder objects) by encouraging the use of substances to prevent agglomeration of the powder components.

Moreover, the Examiner's argument that "added water is not seen as required after formation of an object" improperly ignores the word "powder" in Applicants' claims. The explicit language of independent Claims 40, 43, and 103 specifies that the object is a "compressed powder" object. If water was added prior to formation of the compressed object, it would not be a "compressed powder object." Accordingly, Applicants request that the novelty rejection of Claims 40, 43, 103, 111-120, and 126-134 be withdrawn.

With respect to the second group of claims, the present Office Action contains no discussion of the teachings in Brown that the Examiner considers relevant to poorly crystalline apatitic calcium phosphates and/or molded calcium phosphate pastes, as recited in independent Claims 42 and 138. In fact, the Office Action includes only the following, potentially-relevant, summary conclusion: "the Brown Product however, as the mixed product of Ca Carbonate and Ca Phosphate, is in fact the same as the instant object" (Office Action, page 4). Brown, however, contains no mention or suggestion of a poorly crystalline apatitic calcium phosphate. This is because Brown's disclosure is devoted exclusively to the preparation of compositions that produce hydroxyapatite *in vivo*. Hydroxyapatite and poorly crystalline apatitic calcium phosphate are distinct substances. As explained in Applicants' disclosure, "[t]he poorly crystalline apatitic calcium phosphate of bone is distinguished from the more crystalline hydroxyapatites and non-stoichiometric hydroxyapatites by its distinctive XRD pattern as shown in Figure 7" (page 1, lines 27-30). Applicants request, therefore, that the novelty rejection of

Claims 42, 138-145, and 148 be withdrawn or that the Examiner specify those passages within Brown that he believes relevant to the anticipation of the rejected claims.

IV. Rejections Under 35 U.S.C. §103(a) Over Brown *et al.* (U.S. Patent No. 6,201,039) or Constantz (U.S. Patent No. 5,962,028) in view of Fukase *et al.* (1990) *J. Dent. Res.* 69(12):1852-1856 and Tung (U.S. Patent No. 5,037,639).

Claims 40, 42, 43, 103, and 111-151 have been rejected under 35 U.S.C. §103(a) as allegedly obvious over Constantz or Brown in view of Fukase *et al.* (1990) *J. Dent. Res.* 69(12):1852-1856 (hereinafter "Fukase") and U.S. Patent No. 5,037,639 to Tung (hereinafter "Tung"). The teachings of Constantz and Brown are discussed above.

Fukase investigates the properties of calcium phosphate pastes formed of tetracalcium phosphate (TTCP) and anhydrous dicalcium phosphate (DCPA) (page 1852, col. 2). Tung teaches the rapid precipitation of amorphous calcium phosphate (ACP) from solution and its crystallization into apatite (col. 3, line 67 – col. 4, line 7). Neither of these references teaches or suggests compressed powder objects or poorly crystalline apatitic calcium phosphate, nor does the Examiner make any attempt to suggest they do so (Office Action, page 5).

Thus, Fukase and Tung, alone or in combination, cannot remedy the shortcomings of Constantz and Brown discussed above. Given that neither Constantz nor Brown teaches or suggests compressed powder objects or poorly crystalline apatitic calcium phosphates (a point practically conceded by the Examiner at page 5 of the Office Action), the cited art fails to teach or suggest every limitation of independent Claims 40, 42, 43, 103, and 138. Accordingly, Applicants respectfully request that the obviousness rejection of pending Claims 40, 42, 43, 103, and 111-151 be reconsidered and withdrawn.

V. Conclusion

In view of the foregoing remarks, it is submitted that Claims 40, 42-43, 103, and 111-151 are in condition for allowance, which action is earnestly solicited. The Examiner is invited to contact the undersigned by telephone should any issues remain outstanding.

A Petition for a three-month extension of time, extending the period for response up to and including July 17, 2003, is included with this Amendment and Reply, as is an authorization to charge our Deposit Account No. 08-0219 the associated fee of $460.00 pursuant to 37 C.F.R. § 1.17(a)(3). No additional fees are believed due. However, in the event that any fees are due in connection with this application, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 08-0219.

Respectfully submitted,

Date: July 17, 2003

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